homocystinuria

Homocystinuria is an inherited disorder in which the body is unable to process certain building blocks of proteins (amino acids) properly. There are multiple forms of homocystinuria, which are distinguished by their signs and symptoms and genetic cause. The most common form of homocystinuria is characterized by nearsightedness (myopia), dislocation of the lens at the front of the eye, an increased risk of abnormal blood clotting, and brittle bones that are prone to fracture (osteoporosis) or other skeletal abnormalities. Some affected individuals also have developmental delay and learning problems.

Less common forms of homocystinuria can cause intellectual disability, failure to grow and gain weight at the expected rate (failure to thrive), seizures, problems with movement, and a blood disorder called megaloblastic anemia. Megaloblastic anemia occurs when a person has a low number of red blood cells (anemia), and the remaining red blood cells are larger than normal (megaloblastic).

The signs and symptoms of homocystinuria typically develop within the first year of life, although some mildly affected people may not develop features until later in childhood or adulthood.

Frequency

The most common form of homocystinuria affects at least 1 in 200,000 to 335,000 people worldwide. The disorder appears to be more common in some countries, such as Ireland (1 in 65,000), Germany (1 in 17,800), Norway (1 in 6,400), and Qatar (1 in 1,800). The rarer forms of homocystinuria each have a small number of cases reported in the scientific literature.

Genetic Changes

Mutations in the *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* genes cause homocystinuria.

Mutations in the *CBS* gene cause the most common form of homocystinuria. The *CBS* gene provides instructions for producing an enzyme called cystathionine beta-synthase. This enzyme acts in a chemical pathway and is responsible for converting the amino acid homocysteine to a molecule called cystathionine. As a result of this pathway, other amino acids, including methionine, are produced. Mutations in the *CBS* gene disrupt the function of cystathionine beta-synthase, preventing homocysteine from being used properly. As a result, this amino acid and toxic byproducts substances build up in the blood. Some of the excess homocysteine is excreted in urine.

Rarely, homocystinuria can be caused by mutations in several other genes. The enzymes made by the *MTHFR*, *MTR*, *MTRR*, and *MMADHC* genes play roles in converting homocysteine to methionine. Mutations in any of these genes prevent the enzymes from functioning properly, which leads to a buildup of homocysteine in the body. Researchers have not determined how excess homocysteine and related compounds lead to the signs and symptoms of homocystinuria.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

Although people who carry one mutated copy and one normal copy of the *CBS* gene do not have homocystinuria, they are more likely than people without a *CBS* mutation to have shortages (deficiencies) of vitamin B12 and folic acid.

Other Names for This Condition

- cystathionine beta synthase deficiency
- homocysteinemia

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Increased methionine
  https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Methionine.pdf

Formal Treatment/Management Guidelines

- British Inherited Metabolic Disease Group: HCU Clinical Management Guidelines
  http://www.bimdg.org.uk/store/enbs//HCU_clinical_management_guidelines_v12_Jan_2017_375588_17012017.pdf
- British Inherited Metabolic Disease Group: Homocystinuria (HCU) Dietetic Management Pathway
  http://www.bimdg.org.uk/store/enbs//HCU_Dietetic_Management_Pathway_V1_April_2015_215380_12052015.pdf

Genetic Testing

- Genetic Testing Registry: Homocysteinemia due to MTHFR deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1856058/
- Genetic Testing Registry: Homocystinuria due to CBS deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3150344/

- Genetic Testing Registry: Homocystinuria-Megaloblastic anemia due to defect in cobalamin metabolism, cblE complementation type
https://www.ncbi.nlm.nih.gov/gtr/conditions/C1856057/
- Genetic Testing Registry: Homocystinuria, cblD type, variant 1
https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848553/
- Genetic Testing Registry: METHYLCOBALAMIN DEFICIENCY, cblG TYPE
https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855128/
- Genetic Testing Registry: Methylmalonic acidemia with homocystinuria cblD
https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848552/
- Genetic Testing Registry: Methylmalonic aciduria, cblD type, variant 2
https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848554/

Other Diagnosis and Management Resources

- Baby's First Test
http://www.babysfirsttest.org/newborn-screening/conditions/homocystinuria
- GeneReview: Disorders of Intracellular Cobalamin Metabolism
https://www.ncbi.nlm.nih.gov/books/NBK1328
- GeneReview: Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
https://www.ncbi.nlm.nih.gov/books/NBK1524
- MedlinePlus Encyclopedia: Homocystinuria
https://medlineplus.gov/ency/article/001199.htm
- National Organization for Rare Disorders (NORD) Physician's Guide
http://nordphysicianguides.org/wp-content/uploads/2012/02/Homocystinuria_11_29b.pdf
- New England Consortium of Metabolic Programs
http://newenglandconsortium.org/for-families/other-metabolic-disorders/amino-acid-disorders/homocystinuria/

General Information from MedlinePlus

- Diagnostic Tests
https://medlineplus.gov/diagnostictests.html
- Drug Therapy
https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
https://medlineplus.gov/geneticcounseling.html

- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Homocystinuria
  https://medlineplus.gov/ency/article/001199.htm
- Health Topic: Amino Acid Metabolism Disorders
  https://medlineplus.gov/aminoacidmetabolismdisorders.html
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html

Genetic and Rare Diseases Information Center

- Homocystinuria
  https://rarediseases.info.nih.gov/diseases/10770/homocystinuria

Educational Resources

- CLIMB: Homocystinuria Information Sheet
  http://www.climb.org.uk/IMD/Hotel/Homocystinuria.pdf
- Disease InfoSearch: Homocysteinemia
  http://www.diseaseinfosearch.org/Homocysteinemia/3460
- Illinois Department of Public Health
  http://www.idph.state.il.us/HealthWellness/fs/homocystinuria.htm
- MalaCards: homocystinuria
  http://www.malacards.org/card/homocystinuria
- Michigan Department of Community Health: What is Homocystinuria?
  http://www.michigan.gov/documents/Homocystinuria_157137_7.pdf
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Homocystinuria&type=profile
- New England Consortium of Metabolic Programs
  http://newenglandconsortium.org/for-families/other-metabolic-disorders/amino-acid-disorders/homocystinuria/
- Orphanet: Classic homocystinuria
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=394

- Orphanet: Homocystinuria due to methylene tetrahydrofolate reductase deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=395
- Orphanet: Methylcobalamin deficiency type cblE
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2169
- Orphanet: Methylcobalamin deficiency type cblG
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2170
- Screening, Technology, and Research in Genetics
  http://www.newbornscreening.info/Parents/aminoaciddisorders/CBS.html
- Virginia Department of Health
  http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_HCU_English.pdf

Patient Support and Advocacy Resources

- Children Living with Inherited Metabolic Diseases (CLIMB) (UK)
  http://www.climb.org.uk/
- CLIMB: Children Living with Inherited Metabolic Diseases
  http://www.climb.org.uk/
- HCU Network Australia
  http://hcunetworkaustralia.org.au/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/homocystinuria-due-to-cystathionine-beta-synthase-deficiency/
- Resource list from the University of Kansas Medical Center: Metabolic Conditions
  http://www.kumc.edu/gec/support/metaboli.html

GeneReviews

- Disorders of Intracellular Cobalamin Metabolism
  https://www.ncbi.nlm.nih.gov/books/NBK1328
- Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK1524

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22homocystinuria%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Homocystinuria%5BMAJR%5D%29+AND+%28homocystinuria%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

OMIM

- HOMOCYSTINURIA DUE TO CYSTATHIONINE BETA-SYNTHASE DEFICIENCY
  http://omim.org/entry/236200
- HOMOCYSTINURIA DUE TO DEFICIENCY OF N(5,10)-METHYLENETETRAHYDROFOLATE REDUCTASE ACTIVITY
  http://omim.org/entry/236250
- HOMOCYSTINURIA-MEGALOBLASTIC ANEMIA, cblE COMPLEMENTATION TYPE
  http://omim.org/entry/236270
- HOMOCYSTINURIA-MEGALOBLASTIC ANEMIA, cblG COMPLEMENTATION TYPE
  http://omim.org/entry/250940
- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE
  http://omim.org/entry/277410

Sources for This Summary

- Adam S, Almeida MF, Carbasius Weber E, Champion H, Chan H, Daly A, Dixon M, Dokoupil K, Egli D, Evans S, Eyskens F, Faria A, Ferguson C, Hallam P, Heddrich-Ellerbrok M, Jacobs J, Jankowski C, Lachmann R, Lilje R, Link R, Lowry S, Luyten K, MacDonald A, Maritz C, Martins E, Meyer U, Müller E, Murphy E, Robertson LV, Rocha JC, Saruggia I, Schick P, Stafford J, Stoelen L, Terry A, Thom R, van den Hurk T, van Rijn M, van Teefelen-Heithoff A, Webster D, White FJ, Wildgoose J, Zweers H. Dietary practices in pyridoxine non-responsive homocystinuria: a European survey. Mol Genet Metab. 2013 Dec;110(4):454-9. doi: 10.1016/j.ymgme.2013.10.003. Epub 2013 Oct 10.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24206934
- Carmel R, Green R, Rosenblatt DS, Watkins D. Update on cobalamin, folate, and homocysteine. Hematology Am Soc Hematol Educ Program. 2003:62-81. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14633777
- El-Said MF, Badii R, Bessisso MS, Shahbek N, El-Ali MG, El-Marikhie M, El-Zyoid M, Salem MS, Bener A, Hoffmann GF, Zschocke J. A common mutation in the CBS gene explains a high incidence of homocystinuria in the Qatari population. Hum Mutat. 2006 Jul;27(7):719.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16786517
- Elsaid MF, Bener A, Lindner M, Alzyoud M, Shahbek N, Abdelrahman MO, Abdoh G, Bessisso MS, Zschocke J, Hoffmann GF. Are heterocygotes for classical homocystinuria at risk of vitamin B12 and folic acid deficiency? Mol Genet Metab. 2007 Sep-Oct;92(1-2):100-3. Epub 2007 Aug 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17686644

- GeneReview: Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency https://www.ncbi.nlm.nih.gov/books/NBK1524
- Moat SJ, Bao L, Fowler B, Bonham JR, Walter JH, Kraus JP. The molecular basis of cystathionine beta-synthase (CBS) deficiency in UK and US patients with homocystinuria. Hum Mutat. 2004 Feb; 23(2):206.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14722927

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/homocystinuria

Reviewed: March 2016
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services